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This is the second annual report on a randomized, double-blind, placebo-controlled clinical trial of 130 consecutive breast cancer patients who are being studied over four successive chemotherapy treatments to assess if an antidepressant drug can attenuate or prevent the development of fatigue in women during chemotherapy treatment. We are also examining the potential role of depression, sleep disturbance and the cytokine TNF-α in the development of fatigue during chemotherapy treatment. Patients are randomized to take the antidepressant paroxetine (Paxil®) or placebo once a day during the trial. They complete standardized psychometric measures of fatigue and depression on the 7th day following each of the four chemotherapy cycles. Patient motion is assessed as a concomitant measure of fatigue by ambulatory electronic monitoring during the second and fourth assessments. Blood levels of TNF-α are also measured at these two treatments.

Patient accrual began at the first site in November, 1996. In order to maximize our accrual, we opened the study at a second site (Highland Hospital) in October 1997 and began accrual at a third site (Strong Memorial Hospital) in July 1998. We anticipate that opening the study at this third site will enable us to meet our target of 100 evaluable patients.

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Preventing Fatigue in Patients with Breast Cancer Treated with Chemotherapy

INTRODUCTION

Subject

Second annual report on a clinical trial of breast cancer patients to test the hypothesis that Preventing Fatigue in Patients with Breast Cancer Treated with Chemotherapy administering antidepressant medication during chemotherapy treatment can prevent the development of treatment-induced fatigue.

Purpose

Fatigue is the most commonly reported treatment side effect of chemotherapy for breast cancer. Fatigue has been found to be up to seven times more prevalent in cancer patients than the general population.[1] It is frequently reported to begin with treatment, continue through the course of chemotherapy and often persist following treatment completion. We studied 1048 consecutive outpatients treated solely with chemotherapy over five successive treatments and found that 81% of women with breast cancer reported fatigue. It was the most common side effect the women experienced. The adverse effects of fatigue are frequently underestimated and thus go untreated.[2,3] In addition to being pervasive, persistent, debilitating and discouraging, chemotherapy treatment-induced fatigue may have serious consequences for the breast cancer patient's quality of life and ability to actively participate in their treatment.

Fatigue can affect compliance with potentially curative treatment for breast cancer. Fatigue is a common reason given by cancer patients who refuse to enter experimental protocols.[4] Some women undergoing chemotherapy for breast cancer have been found to experience a loss of attention capacity on neurocognitive tests during treatment.[5,6] This impairment may reduce a patients' ability to make decisions regarding her treatment options and their effect on her well-being.[7] Since fatigue can challenge a patients' ability to complete recommended treatment on the optimal schedule,[8] it is apparent that fatigue may indeed reduce a woman's chance for curative cancer therapy.

Fatigue interferes with a patient's quality of life. Treatment-induced fatigue can quite significantly reduce a patient's participation in leisure activities, capacity to sustain meaningful relationships with spouse and family, and ability to work. Patients may be placed in a dependent posture of having to depend on others for home management, transportation and even simple self care activities such as preparing food or bathing.

There has been little systematic research on the pattern of development, etiology or treatment of fatigue during chemotherapy treatment for breast cancer. An effective treatment for chemotherapy-induced fatigue in women with breast cancer holds promise for increasing not only quality of life but also compliance with treatment and thus prognosis for cure. A better understanding of potential mechanisms of chemotherapy induced fatigue could lead to improved pharmacological and perhaps behavioral control of this debilitating symptom commonly experienced by women during treatment for breast cancer.

Our research will address three technical objectives: i) to assess if an antidepressant drug can attenuate or prevent the development of fatigue in women during chemotherapy treatment for breast cancer; ii) to systematically investigate the role played by depression, both as a categorical diagnosis and a dimensional construct, in the development of fatigue during chemotherapy treatment and iii) to extend pilot data that show an association between the cytokine TNF-α and patient reported fatigue.

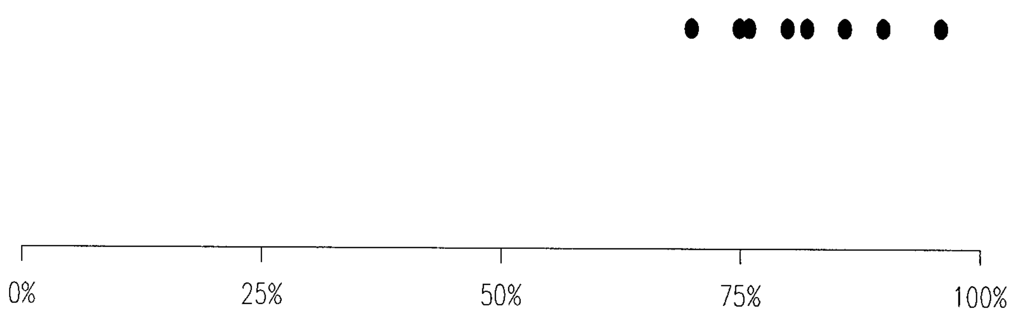
Research Scope

We are conducting a randomized, double-blind, placebo-controlled clinical trial with 130 consecutive breast cancer patients who will be studied over four successive chemotherapy treatments. Patients will be randomized to take the antidepressant paroxetine (Paxil®) or placebo once a day during the trial. They will complete measures of fatigue (the Fatigue Symptom Checklist, the Profile of Mood States (POMS) fatigue subscale and the Multidimensional Assessment of Fatigue) and depression (POMS depression subscale, Hamilton Depression Inventory, and the Center for Epidemiological Studies Depression Scale) on the 7th day following each of the four chemotherapy cycles. The MANE (Morrow Assessment of Nausea and Emesis) will be completed for each of the four treatments and a measure of expectations for side-effects will be given prior to the first on study treatment. Patient motion will be assessed as a concomitant measure of fatigue by ambulatory electronic monitoring during the second and fourth assessments. Patient blood, drawn as part of the normal lab work prior to each chemotherapy treatment, will be used for pregnancy testing for women who have child bearing potential, and at the second and fourth study treatments will be analyzed for TNF-α levels. Multivariate and univariate repeated-measures comparisons of drug vs. placebo data will examine the effectiveness of the intervention. Statistical modeling and exploratory data analytic approaches will examine the potential role of depression and TNF-α in the development of fatigue induced by the treatment of breast cancer in women by chemotherapy.

Background

Fatigue is a very common and troublesome side effect experienced by women during chemotherapy treatment for breast cancer. This prevalent and important problem has been largely overlooked. There is little systematic controlled research on either the etiology or treatment of fatigue during treatment for breast cancer. Winningham et al.[2] summarized in a recent review: "Despite its frequent occurrence, fatigue associated with chemotherapy is poorly understood"[(pp 27.)]. A sizable number of potential variables have been hypothesized to be involved in the development of fatigue; very few have been experimentally investigated. Only a select few can be included in any study without unduly burdening patients. Past studies are supported by our pilot data that suggest psychological depression and the cytokine TNF-α are involved in the development of chemotherapy induced fatigue.

Fatigue is the most common symptom experienced by patients with cancer.[10-12] It is up to seven times more prevalent in cancer patients than in the general population.[1] Cancer patients frequently report that fatigue begins with treatment, continues during the course of chemotherapy, and declines somewhat but persists at a higher-than-baseline rate after treatment is over.[13-15] The figure below summarizes the percent of patients in seven studies[16-22] (with a variety of diagnoses receiving various chemotherapy treatments) who reported fatigue.



Our data from a series of 1048 consecutive outpatients treated solely with chemotherapy for histologically verified oncologic disease at the four hospitals of the University of Rochester Cancer Center and at 15 geographically diverse private practice sites that form a part of our affiliated network of Community Clinical Oncology Program (CCOP) members further support the findings shown above. Patients completed a standardized checklist of 31 common treatment side effects based on the Boston System for Adverse Side Effects. Fatigue was reported by 70% of all patients and 81% of women with breast cancer.[23] No relationship was found between the reporting of fatigue and the utilization or effectiveness of the antiemetic regimen ($p>.05$) suggesting that fatigue is not a side effect of antiemetic drugs. Age was related to fatigue; a significantly higher proportion of patients (74%) below the sample median age of 53 reported fatigue compared to 64% of patients above the median age; ($p<.05$). In a smaller series of patients Piper [(29)] found no association between fatigue and age.

The high prevalence of fatigue has been further supported in a second, separate randomized clinical trial of ours where eighty-three percent of the 142 patients currently entered have reported fatigue by their second chemotherapy treatment. Unfortunately, fatigue is often accepted as a "normal" part of cancer treatment by medical staff. Its adverse effects are frequently underestimated[19] and thus go untreated. In addition to being pervasive, persistent, debilitating and discouraging[18] chemotherapy treatment induced fatigue may have serious consequences for the breast cancer patients' quality of life and ability to actively participate in their treatment.[2,8]

Fatigue interferes significantly with a patient's quality of life in many areas.[24-26] It can reduce breast cancer patients' ability to participate in leisure activities,[27] their capacity to sustain meaningful relationships and activities with their families,[28] to work, and to engage in social and other activities during and after treatment.[25,5] It also places them in a position of depending on others for home management, transportation and even simple self-care activities such as preparing food or bathing.[5,7] This change in daily activity and self-sufficiency may be demoralizing and discouraging. Furthermore, in addition to the activities in which fatigued patients are unable to participate, patients frequently must engage in unwanted activities such as lying down or taking naps in an attempt to cope with their fatigue.[29]

Fatigue is a common reason given by cancer patients who refuse to enter experimental protocols.[4] Cimprich[6] found that women with breast cancer undergoing chemotherapy experienced a significant loss in attention capacity on neurocognitive tests during treatment. This impairment may reduce a patient's ability to make decisions regarding her treatment options and their effect on her well-being.[7] When added to the fact that fatigue also often challenges a patient's ability to complete recommended treatment on the optimal schedule,[8,9] the potential that fatigue has to reduce a woman's chance for curative treatment is apparent.

Although fatigue is a nearly ubiquitous symptom associated with cancer and its treatment, no single definition of fatigue has gained complete acceptance.[2,30] Fatigue is seen as a different concept than tiredness, which is typically expected at a certain time of day or after activity, and which disappears after a short rest or a good night's sleep. In contrast, fatigue is typically reported by breast cancer patients to be an unusual, excessive, and pervasive whole-body experience which is disproportionate or unrelated to activity or exertion and is furthermore not helped by rest or sleep.[29] Fatigue is commonly viewed as a multidimensional construct (similar to pain[31]) which has clinical characteristics that can be conceptualized and measured in several dimensions. Based on this rationale, we will assess fatigue with both subjective and objective measures.

Definitive simple causal relationships between single factors and fatigue outcomes have not been found.[1,2,3,10,32] The likelihood that a combination of mechanisms is involved in the development of fatigue is consistent with most current models such as the Aistairs Organizing Framework[33] Piper's Integrated Fatigue Model (IFM)[29] and Winningham's Psychobiologic-Entropy Hypothesis (PEH).[9] The relationship between chemotherapy treatment and fatigue is likely to involve general physiological processes, specific factors related to treatment, and the influence of depressive disorders.

Data reviewed below show that fatigue is strongly associated with depression.[14,33,34] Fatigue is one of the diagnostic criteria of DSM IV depressive disorders, including major depression and dysthymia.[35] Chen found in a cross-sectional study that adults who experience depression are five to seven times as likely to feel fatigued[1] than adults who do not. In medical patients, depression has been strongly associated with fatigue experienced by patients in intensive care[36] and with fatigue in patients undergoing ambulatory care.[11]

Results from several converging areas of research support a role for depression as a major factor in the etiology of fatigue commonly found in chemotherapy patients: 1) There is a high frequency of depression in cancer patients undergoing chemotherapy. 2) Several studies have found a significant positive correlation between depression and treatment induced fatigue. 3) An intervention study showed that reducing depression decreased patient symptoms of fatigue. The first two areas are detailed below. The intervention study is described as part of our pilot data in the section that follows.

There is a high frequency of depression in cancer patients. The table below shows the percentage of cancer patients undergoing treatment and experiencing depression in five studies[7,20,37,38,39] that used a structured clinical interview to classify depression by DSM-IIIR criteria for depression. Depression was found in 40% to 82% of patients, with a mean percentage of patients with depression (weighted by the number of people per study) of 58%.

Table 1. Percentage of Cancer Patients Reporting Depression in Five Studies (N=311)

	N	Frequency
Mitchell & Glickman[39]	50	82%
Peck & Boland[37]	50	74%
Devlen et al.[7]	120	40%
Nerenz et al.[20]	61	61%
Kubricht[38]	30	56%
Mean Weighted Incidence		**58%**

There is a significant positive correlation between depression and treatment induced fatigue. Blesch et al.[14] found a correlation of r=0.46 between depressed mood and fatigue in 77 lung and breast cancer patients receiving chemotherapy or radiation treatment. Piper et al.[40] also found a significant association (r=0.49, p<.01) between depressed mood and fatigue in a sample of breast and lung cancer patients. Jamar[16] found a significant correlation (r=0.94) between fatigue and depression in women with ovarian cancer undergoing chemotherapy.

In a study of women with breast cancer undergoing six cycles of chemotherapy, Piper[29] reported that out of all variables measured, depression (measured by the Profile of Mood States: POMS depression scale) had the largest and most consistent association with fatigue following each chemotherapy cycle. Depending on the treatment cycle, the correlation of depression with fatigue ranged from r=0.50 to r=0.80. Depression accounted for 10% to 64% of the unique variance in the number of fatigue symptoms reported concurrently and 7% to 58% of the unique variance in the intensity of fatigue concurrently reported on the Fatigue Symptom Checklist (FSCL).[41]

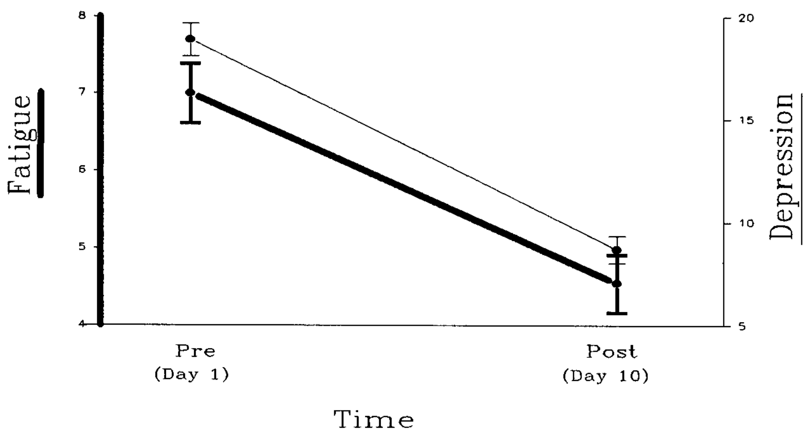
Fatigue reported after patients' second chemotherapy treatment was significantly related to their ratings of depression following their first chemotherapy treatment in a study of ours where 451 consecutive cancer patients have been studied to date. Patients reporting fatigue had mean depression values on the Symptom Checklist-90 (SCL-90) close to one standard deviation above those of patients without reported fatigue ($M=58.7 \pm 8.8$ vs. $M=49.1 \pm 10.4$; $t=9.6$; $p<0.01$). They also had significantly more previous depressive affect on the Profile of Mood States (POMS; $t=6.1$; $p<.01$). The significant relationship was also found in subgroup analyses of breast cancer patients.[23]

Psychological depression as measured by either symptoms (SCL-90) or mood (POMS) appears related to subsequent chemotherapy-induced fatigue. A finding that patient-reported depression correlated with subsequent patient reported fatigue suggests, but does not prove, a causal link. The proposed study will analyze repeated measures of depression and fatigue by cross-lagged statistical procedures described later. Current pilot data support an association; research proposed here will begin a further systematic examination of this association.

A previously reported clinical trial in which our research team participated with the Psychosocial Collaborative Oncology Group, studied a sample of cancer patients for whom alprazolam (Xanax®) was administered over a ten day period[42] to reduce depression (measured by the Hamilton Depression Rating Scale). A post-hoc re-analysis of data from this study shows that fatigue was reduced along with depression.

Since the trial was not designed to assess fatigue, no specific fatigue measure was used. A measure of fatigue was constructed post-hoc from the various assessment instruments not including the instruments used to measure depression. Five questions were selected that were quite similar to questions commonly found in existing scales that measure fatigue.[29,41,43,44] The following questions appeared to have face validity as measures of fatigue: "Feeling low on energy or slowed down," "Feeling weak in parts of your body," "Heavy feelings in your arms or legs," "Feeling everything is an effort," "Slowness of thought and speech; impaired ability to concentrate; decreased motor activity." The five questions were found to be conceptually coherent with a Cronbach α internal consistency coefficient of 0.78.

Seventy-one patients receiving the drug alprazolam were originally reported to have a significant decrease ($p<.01$) in both self-report and clinician-rated depressive mood over a ten day period. In the re-analysis, we also found a significant reduction on the post-hoc measure of fatigue over the ten day study ($p<.001$). The significant decrease was also shown through an analysis of covariance with patients' depression scores used as a covariate. It appears that the antidepressant medication had an independent effect on the post-hoc measure of fatigue separate from its effect on depression. These results are shown in the figure below. The heavy solid line represents the re-analyzed data.



Comparative data on the reduction of depression reported in the original manuscript are shown by the lighter line. While suggestive, findings using the post-hoc scale need to be viewed cautiously since the items were chosen for their face validity. Some questions may measure depression as well as fatigue.

Many variables have been hypothesized to be involved in the development of the fatigue found in women treated for breast cancer; few have been systematically investigated. Evidence that elevated production of cytokines is related to fatigue comes from studies that have noted that marked fatigue can develop following therapeutic administration of cytokines including TNF-α. TNF-α has also been associated with loss of muscle protein and decreased muscle contractility which may result in increased feelings of fatigue and reduced physical activity.[2,32,45] Our recent pilot work supports this relationship. We found that TNF-α levels fell significantly over 3 cycles of chemotherapy in five patients receiving the drug Trental® but not in 10 patients receiving placebo (p=0.04) who were entered in a randomized clinical trial examining interventions for enhancing quality of life in cancer patients with recurrent disease. We also measured a TNF-α increase of 71% over roughly four months in a pilot series of six cancer patients with recurrent disease. Patient self-reported fatigue paralleled this increase. Over the same time frame, scores on the POMS fatigue subscale increased 18%, fatigue items from the FACT-G measure of quality of life increased 17%, a visual analogue scale scores of tiredness from the Edmonton Symptom Assessment Scale (ESAS) increased 43%, values from a visual analogue scale of the ESAS assessing drowsiness increased 78%.

he association of selective cytokine activation, including that of TNF-α, with fatigue in patients with Chronic Fatigue Syndrome as shown by the work of Borish[32] and colleagues, its known role in production of cancer-related anorexia and cachexia and our preliminary evidence from an ongoing research study of the ability of Trental® to lower serum levels of the cytokine in patients receiving chemotherapy for metastatic malignancies provide a rationale for repeated measurement of serum levels of TNF-α in cancer patients receiving chemotherapy to further elucidate the etiology of fatigue in cancer patients undergoing treatment.

Body of Report

Technical Objectives

Specific Aim 1: To assess the degree to which an antidepressant drug can attenuate or prevent the development of patient fatigue during chemotherapy treatment for breast cancer.

Specific Aim 2: To systematically investigate the role played by depression, both as a categorical diagnosis and a dimensional construct, in the development of fatigue during chemotherapy treatment.

A Secondary, exploratory aim is to extend pilot data that show an association between the cytokine Tumor Necrosis Factor (TNF-α) and fatigue, and their associations with depression in subjects with breast cancer.

Experimental Methods

Overview: Meaningful ideas that influence theory and clinical practice evolve over time from careful research that builds on past research findings and thus strengthens their validity. This research is a step in that process. In developing this study, we have built on the literature and relevant work completed by other research teams, and on our research background in studies with cancer patients in the areas of: 1) problem identification;[46] 2) psychosocial assessment techniques;[47] 3) methodology;[48] 4) evaluation of psychosocial and behavioral interventions to control treatment side effects; and 5) implementation of cancer control interventions.[49,50]

Design: Patients are stratified by chemotherapy treatment and randomized to either drug or placebo. Assessments are made seven days following chemotherapy administration over four successive chemotherapy treatments. Fatigue is generally reported by patients to be the most severe within the seven days following chemotherapy, the time of maximum chemotherapy effect on hematological parameters such as hematocrit and hemoglobin. Anemia is frequently but not always associated with the presence of fatigue,[59] and Piper[29] found no association between fatigue and changes in hematocrit and hemoglobin levels following chemotherapy.

Nonetheless, illness related clinical factors such as hematocrit, hemoglobin, renal function, calcium, weight and other measures gathered as part of normal clinic procedure will be recorded for potential use in exploratory, subgroup secondary analyses following the planned statistical analyses of data to address the two proposed and one exploratory aims.

The antidepressant or placebo is taken once a day from day 7 following study treatment one until day 7 following study treatment four. Treatments are typically 3 to 4 weeks apart — thus there is an adequate time for the antidepressant to reach a therapeutic level. While the data are not conclusive, fatigue may vary with type of chemotherapy treatment. The contradictory results found in previous studies of correlates of fatigue[52-55] may have been influenced by this variability. To help control this potential confound, patients will be stratified based on chemotherapy treatment (Cyclophosphamide, Methotrexate, 5-Fluorouracil:CMF or Cyclophosphamide, Adriamycin, 5-Fluorouracil:CAF or other).

The study ends at the assessment seven days after the fourth on study chemotherapy treatment. Patients will be asked if they wish to continue taking the pills. The percent of patients who would choose to remain on each of the arms will be recorded as a descriptive clinical outcome measure. It is anticipated that more patients taking the antidepressant will wish to continue than those taking the placebo. A patient can have Paxil® prescribed by their treating oncologist at their own expense, if they wish, after completing the study.

Sample: 130 consecutive patients undergoing chemotherapy for breast cancer at any of the four affiliated hospitals of the URCC will be studied. A patient is eligible if she/he is: undergoing chemotherapy treatment for histologically confirmed breast cancer; able to swallow medication; able to understand and speak English (since the standard assessment psychosocial instruments used here are only available in English versions); not presently taking psychotropic medication; not currently pregnant or nursing; and is currently scheduled for at least four cycles of chemotherapy (a typical treatment course with CMF or CAF is six cycles). A patient will be excluded if she/he has: impaired renal, hepatic or cardiac function (as judged by her/his treating medical oncologist), history of seizures, history of mania, or is taking medications for which there are demonstrated interactions with Paxil®. Eligibility will be checked during patient interviews and from patient records at each participating hospital.

Women and minority representation: Previous randomized cancer control trials of our group have enrolled minority patients at a rate (15%) that is higher than for treatment protocols at the URCC (whose enrollment, in turn, matches the minority composition (11%) of the city of Rochester and the surrounding 10 county area). We monitor sample enrollment carefully and will make extra efforts to insure a representative sample of minority women.

Drug Characteristics, Dosage and Administration: Patients randomized to the active arm of this study will receive a standard clinical dose of 20 mg per day of the antidepressant Paroxetine (Paxil®), a potent, selective inhibitor of serotonin reuptake that has little affinity for the catecholaminergic and histaminergic systems. Paroxetine has undergone extensive clinical testing. Caley and Weber[56] reviewed 14 randomized double-blind trials involving 1425 outpatients with moderately severe depression. All 14 trials lasted 6 weeks. Four were placebo-controlled and in the remainder an active drug arm was used with or without a placebo arm. The reviewers concluded that paroxetine is an effective treatment for moderately severe depression. In four trials more than 50% of patients receiving paroxetine demonstrated a 50% or greater reduction in Hamilton Rating Scale for Depression (HRSD) scores over a 6 week period compared to 23% of patients receiving placebo. In 8 of the remaining 10 trials efficacy was comparable to or greater than that of the active drugs.

In another 6-week randomized double blind trial comparing paroxetine with placebo in 167 patients with a major depressive episode, a significant difference in the total HRSD score was apparent between the two groups by the second week of treatment; and by the fourth week there were significant differences in all variables that were measured. In addition, there was a significant difference in the sleep factor of the HRSD by the end of the first week of treatment suggesting that paroxetine had less of an activating than a somnolent effect. Furthermore, more patients reported somnolence than nervousness, even when the frequency of these symptoms in patients taking placebo was accounted for. Improved sleep may act to decrease fatigue.[57] These findings suggest that paroxetine can produce a significant clinical effect during the active study period proposed in this study.

Paroxetine has been found to produce fewer side effects than first generation antidepressants such as the tricyclic agents amitriptyline (Elavil®), imipramine (Trofranil®) or the monoamine oxidase inhibitors (phenelzine: Nardil®) or second generation agents such as trazodone (Desyrel®). The few adverse effects on the central and autonomic nervous systems tend to be more transient than the antidepressants mentioned above and include: sedation, drowsiness, hypotension and anticholinergic effects such as dry mouth, constipation, blurred vision, and urinary retention.

Paroxetine does not impair motor performance, potentiate depressant effects of alcohol or other depressant medications, or disturb cardiac function. The drug is well absorbed from the gastrointestinal tract. Stable plasma concentrations are achieved within 4-14 days of beginning administration, and therapeutic effect is noted typically within four weeks. A mean terminal half-life of 24 hours permits once-daily dosing which can also be an advantage in use with cancer patients who may often be taking other medication and are sometimes reluctant to take several more pills. It is metabolized primarily by the liver, and metabolites are pharmacologically inactive.

Caution will be used in patients receiving oral anticoagulants. Paroxetine will not be given to patients being treated with monoamine oxidase inhibitors or other drugs that increase brain serotonin concentrations. Identical drug/placebo capsules will be prepared by our pharmacy. The placebo capsules are prepared with a filler that consists of 6 ml of D & C red dye #40 (100 mg/ml) added to each 100 gm of lactose, U.S.P.

<u>Measures</u>

To maintain a high level of adherence to the experimental protocol, the total amount of time spent filling out questionnaires must be kept manageable for patients who may be physically and cognitively challenged by their treatment. Patients will complete most instruments at home and mail them back in stamped, self-addressed envelopes, or they will be picked up the next day when the motion monitor (explained below) is picked up at the patient's home. Instruments will be administered one week following chemotherapy treatments, which is the time of greatest reported fatigue.[29] A reminder phone call will be made to patients on the 7th day after treatment ends when the measures are to be completed. Any questions will be answered and the patient will be encouraged to complete the measures that day.

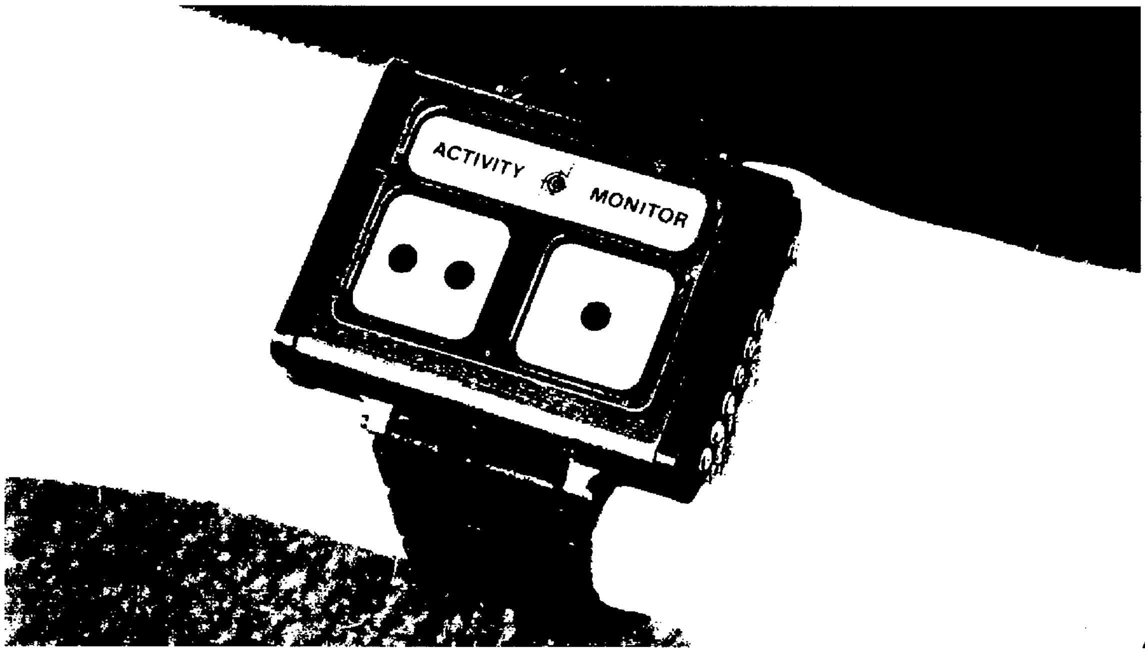
Outcome Measures of Fatigue. The four measures described below will assess fatigue: the Fatigue Symptom Checklist (measures symptoms of fatigue), the monopolar POMS Fatigue/Inertia subscale (measures fatigue as a mood), the Multidimensional Assessment of Fatigue (measures degree of interference in daily living), and the ambulatory monitoring of patient activity (measures changes in daily activity).

- The Fatigue Symptom Checklist (FSCL)[41] Patients indicate the presence and intensity of each of 30 symptom items related to fatigue on a five point scale. Reliability of the three subscales range from 0.77 (drowsiness and dullness) to 0.90 (projection of physical impairment); reliability for the total scores ranges from 0.92 to 0.94. Piper[29] found that the FSCL was completed a higher percentage of times than any other fatigue measure used in her study, including her own Piper Fatigue Scale. We asked ten patients to complete the Piper Fatigue Scale. The majority felt strongly it was "too confusing" and had "far too many questions," so we reluctantly decided not to use it.

- The Fatigue/Inertia (F/I) subscale of the Monopolar Profile of Mood States (POMS) Short Form measures fatigue as a mood through five items with an internal reliability ranging from 0.86 to 0.95 in six population samples.[58] We used it also in the pilot study of TNF-α presented above.

- The revised Multidimensional Assessment of Fatigue (MAF)[59] measures four dimensions of fatigue (severity, distress, interference with daily living tasks, timing) through 16 questions. Internal consistency of 0.93 has been shown in 133 subjects along with convergent and divergent validity.[60,61]

- Ambulatory monitoring of patient activity.[62] Patient motion averaged over selected time spans during a three day period will assess fatigue. Use of this measure is prompted not only by the face validity of the measure (fatigued patients universally report marked reductions in activity) but also the fact that the original clinical diagnosis of Chronic Fatigue Syndrome contained a definition based on reductions in patient activity.[63] Activity will be recorded by the mini-motion logger actigraph from Ambulatory Monitoring, Inc. This is an accelerometer and microprocessor with 32K of dedicated memory that is programmed through an interface device. Shown in the Figure below, it is approximately the size of a wrist watch.



A recent article[64] confirmed its reliability. We will use it to sample patient activity once a minute during the 6th, 7th and 8th days following chemotherapy administration for assessments two and four. Motion data will be analyzed by the approach developed by Oman[65] and the difference between the two assessments will be used as outcome.

Measures of Depression. Because fatigue can be a symptom of depression, measures of depression have been carefully selected to minimize potential confounding and enable assessment of possible confounds between these concepts. We will measure depression both as a categorical diagnosis and as a dimensional construct in order to assess severity using both subjective (CES-D and POMS) and observer rated measures (Hamilton Depression Inventory[HDI]).

- Depressive symptoms will be measured with the Center for Epidemiological Studies Depression Scale (CES-D). The CES-D[66] is a 20-item depression scale developed and validated for use with several populations. It uses a format similar to the Beck Depression Inventory, but with less emphasis on physical symptoms of depression that may be confounded with disease symptoms or treatment side effects. It has been shown to reliably and validly measure depression in cancer populations.[67]

- Categorical diagnosis of depressed mood disorders. Severity of symptoms of depression will also be measured using the Hamilton Depression Inventory (HDI)[68,69]. This instrument comprises 23 items (or symptoms) that are evaluated using 38 questions. This is a recently developed paper and pencil version of the Hamilton Depression Rating Scale (HDRS) and measures the severity of symptoms of depression over the previous two weeks. Completion time is approximately 10 minutes. The first 17 items correspond to those included in the original HDRS developed by Hamilton[70]; six additional items relate to symptoms of major depressive disorder and dysthymia. Validity and reliability were confirmed in a sample of 357 adults (140 with major depression, 99 with anxiety disorder and 118 nonpsychiatric community controls). Cronbach's internal consistency coefficient alpha reliability r_I =. 94 for the total sample. One-week test-retest reliability $r_{tt} = .96$. Convergent, discriminant and contrasted groups (criterion) validity were also demonstrated. Furthermore there was a strong correlation between subject's scores on the HDI and on the HDRS with $r(329) = .95$ indicating that the paper and pencil version (HDI) is equivalent to the version administered by structured clinical interview (HDRS).

- Depressive mood will be measured with the Depression-Dejection subscale of the Profile of Mood States -- Short Version (POMS), which consists of five adjectives. It has been shown to be internally consistent (α=0.91), reliable and valid in a number of psychometric studies.[58]

- Tumor Necrosis Factor-α (TNF-α) serum levels will be measured by ELISA using a standard, commercially available kit from R and D Systems and the URCC laboratory currently running similar analyses for an ongoing study. The sensitivity of this method is 4.4-1000 pg/ml.

Side-effect Measures.

- Patient expectation for side effects will be measured by a questionnaire adapted from one used previously by several researchers.[21,71,72] Its predictive validity is supported by findings that it significantly predicted subsequent development of nausea. Convergent and divergent validity was supported by further ROC analyses showing patient expectation of nausea was significantly predictive ($p < .05$) of future nausea (convergent validity) but that a patient's expectation of any of eleven other specific side effects was not significantly associated with subsequent development of nausea (divergent validity p's >.05).

- Nausea and emesis will be measured by the Morrow Assessment of Nausea and Emesis (MANE). It has been used in two previous URCC CCOP protocols and by several dozen other investigators in studies over the past decade. Psychometric validity and reliability have been reported.[73,74]

- Delayed nausea and delayed emesis are defined as beginning more than 24 hours following completion of chemotherapy with a 24 hour period free of symptoms. They will be measured by a patient report diary developed by Burish and Carey[75,76] and completed by patients over a five-day period.

Statistical Analyses:

Statistical and clinical significance represent two complementary viewpoints of data analysis.[77-79] Clinical significance, while it relies on test statistics, is concerned with the number of patients for which a particular intervention shows some degree of efficacy. Statistical significance focuses on the overall magnitude of treatment efficacy for the group of patients treated by examining separation between mean values for the treated and control groups of patients. Both considerations are important and applicable to aims of this research; both the number of patients who show improvement and the overall magnitude of the improvement are of interest. Taken together, they provide a rational data analysis plan upon which discussion of the data can be more conservatively based than if either viewpoint were taken alone.[80] The method of Andrews et al.[81] will be used to determine any needed transformations to normality before multivariate analyses are performed.

Analysis Plan for Aim One: Complementary parametric statistical approaches will be used to systematically examine the effect of paroxetine on fatigue. Data from the clinical trial will be analyzed through a 2 (group: placebo/drug) x 4 (outcomes: FSCL, POMS, MAF, ambulatory activity) x 4 (time) multivariate repeated measures analysis of variance (MANOVA) followed by appropriate univariate analyses of variance (ANOVAS) as outlined in the table on the next page.

Table 3: Statistical Model for Analyses of Variance

$$Y_{ijt} = \mu + \alpha_i + \gamma_t + \Gamma_{it} + \beta_j + \epsilon_{ijt}$$

Where: $i = 1,2$ (arm)

$t = 1,\ldots4$ (chemotherapy cycle)

$j = 1,\ldots50$ (subject)

$\Sigma_i \alpha_i = \Sigma_t \gamma_t = \Sigma_i \Gamma_{it} = 0$

β_j's iid $N(0,\sigma_\beta^2)$

ε_{ijt}'s N iid $(0,\sigma_\varepsilon^2)$

$[\beta_j]$ indep of $[\varepsilon_{ijt}]$

We will also use a regression based approach used in our earlier study and by others.[82,83] Scores for each subject are regressed on time to yield the intercept, which estimates the true baseline value for each subject, and the slope, which estimates the direction and magnitude of response to treatment for that patient.

This method handles missing data better than an ANOVA approach. It amplifies the reliability of the outcome measures used in testing the hypothesis. Finally, the distribution of the slopes obtained is approximately normal, allowing the use of the most powerful available tests. No substantive differences in the interpretation of results from the two approaches (ANOVA and Regression) are anticipated and similar findings from both will increase confidence in any statistical results.

The clinical significance of the data will be examined by the non-parametric Chi square and Fisher's Exact Test (where appropriate) to statistically compare the proportion of patients who reported fatigue in the group taking paroxetine with the proportion of patients in the group taking placebo.

Analysis Plan for Aim Two: The potential effect of depression and TNF-α on fatigue will be examined through linear modeling using GLIM[84] which is a statistical program to compare model fit parameters as variables are systematically added and removed from a proposed model. A model that hypothesizes a direct link between treatment intervention and fatigue will be tested against a more complex model that hypothesizes depression as an intermediate variable between treatment and fatigue. The single effect of TNF-α will then be added to the model. The fit of each model to the data and whether or not added factors significantly add to the model fit will be statistically tested as each variable is added and/or removed. It is not expected that first (or higher) order interactions will add significant explained variance to the model.

Exploratory analyses of associations among depression, fatigue and TNF-α: The exploratory Aim to extend pilot data on relationships among TNF-α , patient-report fatigue and depression will be tested with exploratory data analytic techniques such as the graphic relationship programs in BMDP Diamond statistical package. Analyses will further investigate previous findings that depression scores early in treatment are associated with future fatigue[23,85] using a lagged regression model with anxiety (measured by the Tension-Anxiety Subscale of the POMS Short Form) and depression as independent variables and fatigue as the dependent variable. It is important to include a measure of anxiety in this analysis to provide discriminant validity. This approach is similar to that used by Nerenz et al.,[20] in a study that showed anxiety changes preceded, not followed, the development of anticipatory nausea. Measures of depression have been selected that do not include physical symptoms of fatigue to control for confounding. Given the sample size, these analyses are not viewed as confirmatory, but rather as adding systematic results to an area with little structured data.

Assumptions

Power Calculations and Anticipated Accrual. Morrow et al.[23] found a difference of about three quarters standard deviation in the level of SCL-90 depression scores between patients experiencing and those not experiencing treatment-related fatigue; the proposed study may find approximately this effect within groups pre-chemotherapy to post-chemotherapy. Holland et al.[42] found a smaller change of approximately one-half a standard deviation in SCL-90 depression scores due to alprazolam intervention. To have an 80% chance of detecting a difference similar to that found in Holland et al. at $\underline{p}<.05$ would require about 50 participants in each group.[42] We will aim to enroll 130 subjects to yield 100 evaluable patients assuming about a 20% dropout (which is consistent with previous trials like this).

Procedures

Eligibility:

1. Patient is undergoing chemotherapy treatment for histologically confirmed breast cancer.

2. Patient is able to swallow medication.

3. Patient is able to understand and speak English.

4. Patient is scheduled for at least four cycles of chemotherapy.

5. Patient is not presently taking psychotropic medication.

6. Patient is not being treated with monoamine oxidase inhibitors or other drugs that increase brain serotonin concentrations.

7. Patient does not have impaired renal, hepatic or cardiac function, (as determined by treating medical oncologist).

8. Patient does not have a history of seizures or mania.

Pregnancy testing: We will do a serum pregnancy test for women who have child bearing potential. The first of these will be done on blood taken normally prior to each chemotherapy treatment. The first will be done prior to taking study drug or placebo and subsequent tests will be done monthly

Investigational Drug Procedures: Patients will be randomized to take the antidepressant paroxetine (Paxil®) or placebo once a day during the trial. (starting on the 7th day after the first on-study chemotherapy treatment until the 7th day after the fourth on-study chemotherapy treatment)

Adverse Events: Any "Serious adverse experience" or "Unexpected adverse experience" as defined below will be reported by telephone (301-619-2165) or (301-619-7114 non-duty hours).

(a) "Serious adverse experience" means any experience that suggests a significant hazard, contraindication, side effect, or precaution. With respect to human clinical experience, a serious adverse drug experience includes any adverse drug experience that is fatal or life-threatening, is permanently disabling, requires inpatient hospitalization, or is a congenital anomaly, cancer, or overdose.

(b) "Unexpected adverse experience" means any adverse experience that is not identified in nature, severity, or frequency in the current investigator brochure; or, if an investigator brochure is not required, that is not identified in nature, severity, or frequency in the risk information described in the general investigational plan or elsewhere in the current application, as amended.

Testing Procedures:

1. Patients will complete measures of fatigue and mood on the 7th day following each of the four on-study chemotherapy treatments. Patients will complete most instruments at home and mail them back in stamped, self-addressed envelopes, or they will be picked up the next day when the motion monitor (explained below) is picked up at the patient's home. A reminder phone call will

be made to patients on the 7th day after treatment ends when the measures are to be completed.

2. Patient will wear a wrist watch sized, battery operated, motion logger to assess extent of daily activities on the 6th, 7th, and 8th days following chemotherapy administration for assessments two and four (a total of six days). Study personnel will deliver and pick up the monitor.

3. Additional blood will be drawn during the normal lab work prior to the second and fourth chemotherapy treatments to test for TNF-α levels.

4. Lab values will be recorded from patients' charts.

Results

Status as of October 1, 1998

1. Patients began accruing to the study at Rochester General Hospital on November 5, 1996 and at Highland Hospital in October 1997.

	November 5, 1996 - October 15, 1997	October 16, 1997- October 1, 1998	Total
Patients with breast cancer screened for eligibility	190	246	436
Patients eligible	54	56	110
Patients contacted	53	54	107
Patients accrued	25	32	57
Adverse Events	0	0	0
Patients completed	17	20	37

2. The study was opened at Strong Memorial Hospital and began accrual in July 1998.

3. Discussions among study personnel concerning progress of study are held on a regular basis.

4. A database has been set up for this study with scanable forms and data are entered as it is received.

5. The daily clinic schedule is monitored two to three times a week

6. No analyses have been made on this data at this point.

Discussion

The study is running very smoothly at this point, although the accrual rate is lower than what we will eventually need to meet our target of 100 evaluable patients by our target date of March, 2000. In order to maximize our accrual, we opened the study at a second site (Highland Hospital) in October 1997 and began accrual at a third site (Strong Memorial Hospital) in July 1998. We anticipate that opening the study at this third site will enable us to meet our target of 100 evaluable patients.

CONCLUSION

We anticipate no problems in completing the study as planned.

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